IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TRIS PHARMA, INC., Plaintiff, v. ACTAVIS LABORATORIES FL, INC., Defendant.	Civil Action No. 14-1309-CFC

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MEMORANDUM OPINION

November 30, 2020
Wilmington, Delaware

COLM F. CONNOLLY
UNITED STATES DISTRICT JUDGE

This Hatch-Waxman patent suit filed by Plaintiff Tris Pharma, Inc. against Defendant Actavis Laboratories FL, Inc. comes to me on remand as a result of the Federal Circuit's decision in *Tris Pharma, Inc. v. Actavis Labs. FL, Inc.* (*Tris II*), 755 F. App'x 983 (Fed. Cir. 2019). In *Tris II*, the Federal Circuit vacated the judgment entered by the now-retired district court judge who originally presided over the case.

Tris alleged at trial that Actavis's generic versions of Quillivant XR®, an extended release liquid formulation of methylphenidate (MPH) for the treatment of Attention Deficit Hyperactive Disorder (ADHD), infringed 21 claims recited in five patents: U.S. Patent Nos. 8,465,765 (the #765 patent), 8,563,033 (the #033 patent), 8,778,390 (the #390 patent), 8,956,649 (the #649 patent), and 9,040,083 (the #083 patent). *Tris Pharma, Inc. v. Actavis Labs. FL, Inc.* (*Tris I*), 276 F. Supp. 3d 226, 230–31 (D. Del. 2017). Actavis challenged the validity of the asserted claims based on obviousness and obviousness-type double patenting. After a five-day bench trial, the original judge found all the asserted claims to be invalid for obviousness under 35 U.S.C. § 103. The judge did not address infringement or double patenting. *See id.* at 249 n.2.

Tris appealed the judge's finding of invalidity for seven of the asserted claims—claims 4 and 10 of the #033 patent, claims 6 and 20 of the #765 patent, and claims 15, 16, and 20 of the #390 patent. The Federal Circuit vacated the judgment "[b]ecause [the judge]'s obviousness decision lack[ed] the requisite fact-finding, and because the [judge] erred in rejecting Tris's evidence of objective indicia of nonobviousness." 755 F. App'x at 993. The Federal Circuit "remand[ed] the obviousness analysis to the district court for further fact-finding." *Id.* It "considered the parties' other arguments [but] f[ound] them unpersuasive." *Id.*

After remand, the case was assigned to me and Actavis dropped its obviousness-type double patenting challenge to the asserted claims. Although I had not observed the witnesses at trial, neither party asked for an opportunity to present testimony so that I could make independent credibility determinations. Instead, both parties insisted that I make the "further fact-finding" called for by the Federal Circuit and any fact-finding with respect to infringement issues based on the existing written record. D.I. 180 at 5; D.I. 181 at 5–6; Tr. of Aug. 25, 2020 Hr'g at 7:16–21.

The parties submitted simultaneous post-remand briefs on the fact-finding issues. Tr. of Apr. 10, 2019 Hr'g at 12:1–4. I have reviewed those briefs, the

parties' post-trial briefing, the trial record, and the Pretrial Order. I set forth below my findings of fact and conclusions of law.

I. BACKGROUND

A. Relevant Pharmacological Concepts

Pharmacology, the study of the interactions between a drug and the body, has two broad areas: pharmacokinetics (PK) and pharmacodynamics (PD). PK is sometimes described as the study of what the body does to a drug. It examines the movement of a drug through the body after administration. Thus, it measures, for example, how fast a drug is absorbed, distributed, metabolized, and ultimately excreted from the body. PD, sometimes described as the study of what a drug does to the body, examines the biochemical, physiologic, and molecular effects of a drug on the body. It measures, for example, the onset, duration, and intensity of a drug's effect on the body. Following the parties' lead, I will often refer to PD characteristics as "clinical effects."

Three PK metrics relevant on remand are C_{max}, T_{max}, and PK profile. C_{max} is the maximum concentration of a drug in the body's blood plasma. T_{max} is the time after administration when C_{max} is reached. A drug's PK profile is the graphed depiction of the drug's concentration in the blood plasma over time. Two PD characteristics relevant on remand are duration and onset of effect.

B. MPH, Quillivant XR®, and the Relevant Asserted Claims

The Federal Circuit provided in its opinion this helpful background statement on MPH, Quillivant XR®, and the seven appealed claims which are now before me on remand:

> MPH is one of the most widely prescribed psychostimulants and has been used to treat ADHD since the mid-1950s. Early formulations of MPH were immediate release (IR) forms of the drug that exhibited clinical benefits within 20 to 60 minutes after dosing and whose effects lasted 2–4 hours. IR forms of MPH, however, had drawbacks because they had to be administered multiple times a day, making it challenging for patients to adhere to the dosing schedule. Sustained release (SR) formulations of MPH were thus developed and available in the early 1980s for greater dosing convenience and patient compliance. But those first-generation SR formulations had their own shortcoming: a slow onset of action. Tris's Quillivant XR® is an extended release formulation of MPH comprising an IR component and a SR component. It is a formulation that achieves a 45-minute therapeutic onset and 12 hours of therapeutic effect.
>
> . . . The[ ] seven appealed claims are: claims 4 and 10 of the [#]033 patent; claims 6 and 20 of the [#]765 patent; and claims 15, 16, and 20 of the [#]390 patent. All of the appealed claims are directed to pharmacokinetic (PK) and pharmacodynamic (PD) properties of the Quillivant XR® extended release formulation. These properties include: (1) an extended duration of action of about 12 hours; (2) a single mean peak PK profile; (3) a T_{max} of about 4 to 5.25 hours (early T_{max}); and (4) a 45-minute onset of action/therapeutic effects. All of the claims on appeal recite, among other properties, a single mean peak PK profile and 12-hour duration of effect limitation. All of the claims except for claim 20 of the [#]765 patent recite

> the early T_{max} limitation, and claim 10 of the [#]033 patent and claim 20 of the [#]765 patent are the only two claims that require a 45-minute onset of action. Claim 10 of the [#]033 patent is thus the only asserted claim that recites all four properties.

Tris II, 755 F. App'x at 984.

Three additional points about the asserted claims require mention. First, all the asserted claims teach a "methylphenidate aqueous extended release oral suspension." #765 patent at claim 1 (37:40–41) (claims 6 and 20 ultimately depend from claim 1); #033 patent at claim 1 (37:45–46) (claims 4 and 10 ultimately depend from claim 1); #390 patent at claim 1 (37:54–55) (claims 15, 16 and 20 ultimately depend from claim 1). The parties and the Federal Circuit treated this aqueous oral suspension limitation as requiring a liquid formulation. I will do the same and for ease of reference will at times call it the "liquid formulation limitation." Second, although claims 10 of the #033 patent and 20 of the #765 patent actually recite an onset of "within 45 minutes," for ease of reference I will follow the Federal Circuit's lead and call this limitation at times the "early onset" or "45-minute onset" limitation. Third, the parties stipulated that "about" means "[v]ariability of as much as 10%." D.I. 78 at A-1. Thus, the extended duration-of-effect limitation of "about 12 hours" is met by a 10.8-hour duration of effect; and the T_{max} range limitation of "about 4 to 5.25 hours" is satisfied by a T_{max} range of 3.6 to 5.78 hours. For ease of reference, I will at times

call these limitations respectively the "12-hour duration" and the "claimed T_{max} range" limitations.

C. The Federal Circuit's Remand Instructions

As noted, the Federal Circuit "remand[ed] the obviousness analysis to the district court for further fact-finding." *Tris II*, 755 F. App'x at 993. In addition to this general instruction, the Federal Circuit directed the district court "to resolve [certain] specific fact issues with an explanation to support those findings." *Id.* at 990. In particular, the Federal Circuit ordered further fact-finding to address whether a liquid MPH formulation with a single mean PK profile, 12-hour duration of effect, and 45-minute onset of action would have been obvious over the prior art. *Id.* at 991. The court directed that this additional fact-finding specifically include findings about whether certain prior art MPH formulations "teach a 45-minute onset of action and 12-hour duration of effect." *Id.* at 989. The court also remanded for "further consideration" the obviousness of a liquid MPH formulation with a single mean peak PK profile, 12-hour duration of effect, and a T_{max} range of 4 to 5.25 hours. *Id.* at 991–92. And it directed the district court to address whether Tris's evidence adduced at trial established that (1) its claimed invention enjoyed unexpected results and (2) there was a long-felt need for a liquid MPH product that does not require swallowing a tablet and has a 12-hour duration of effect and 45-minute onset of action. *Id.* at 992.

II. OBVIOUSNESS

A. Legal Standards

Under § 103 of the Patent Act, codified at 35 U.S.C. § 1 *et seq.*, a patent "may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103 (2006). As the Supreme Court explained in the seminal case *Graham v. John Deere Co.*, 383 U.S. 1 (1966), under § 103, "[a]n invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." *Id.* at 14. Section 103 ensures that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). "Were it otherwise patents might stifle, rather than promote, the progress of useful arts." *Id.* (citing U.S. Const. art. I, § 8, cl. 8).

The Court reaffirmed in *KSR* that the "framework" set out in the following paragraph from *Graham* governs the application of § 103, *id.* at 406:

> While the ultimate question of patent validity is one of law, the [§] 103 condition [of patentability] . . . lends itself to several basic factual inquiries. Under [§] 103, the scope and content of the prior art are to be determined; differences between the prior

> art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Graham, 383 U.S. at 14–15 (citations omitted).

It is clear that under this framework, a district court must consider in an obviousness inquiry the three primary factors identified by the Court in *Graham*: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, and (3) the level of ordinary skill in the pertinent art. Less clear is the role, if any, secondary considerations should play in the analysis.

The logical—some would say necessary—implication of the Court's use of the word "secondary" in *Graham* and its holding that the secondary considerations "might be utilized" and "may have relevancy" is that a district court is permitted—but not required in all cases—to examine such considerations in evaluating an obviousness-based invalidity challenge. The Court seemed to confirm as much in *KSR*, when it noted that "*Graham* set forth a broad inquiry and *invited* courts, where appropriate, to look at any secondary considerations that would prove instructive." *KSR*, 550 U.S. at 415 (emphasis added).

But a district court ignores *Graham*'s "invitation" to examine secondary considerations at its peril. One legal scholar, Harmon, has observed that under Federal Circuit law "[w]e are able now safely to strike the 'may' in the . . . sentence" in *Graham* in which the Court stated that secondary "indicia of obviousness and nonobviousness . . . may have relevancy." Robert Harmon, Cynthia Homan, Laura Lydigsen, *Patents and the Federal Circuit* 245 (13th ed. 2017). Harmon correctly notes that "[t]he Federal Circuit has emphatically and repeatedly held that objective evidence of non-obviousness must be taken into account always and not just when the decisionmaker is in doubt." *Id.* In *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983), for example, the Federal Circuit held that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Id.* at 1538. And in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012), the Federal Circuit reaffirmed that holding, *id.* at 1079, and went on to say that the Supreme Court in *Graham* "did not relegate . . . to 'secondary status'" the "objective factors" the Supreme Court had explicitly identified in *Graham* as "secondary considerations," *id.* at 1078.

It is true that less than a month after *In re Cyclobenzaprine*, a different Federal Circuit panel held in *Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, 678 F.3d

1280 (Fed. Cir. 2012) that because it found that the defendants had "failed to prove that [the challenged patent claim] would have been *prima facie* obvious over the asserted prior art," it "need not address" the "objective evidence" of commercial success, long-felt need, and the failure of others. *Id.* at 1296. But the safer course for a district court faced with an obviousness challenge is to treat *Graham*'s invitation to look at secondary considerations like a subpoena. And, indeed, in this case, the Federal Circuit expressly held that Tris's evidence of objective indicia of obviousness must be considered on remand.

Obviousness is assessed based on the perspective of an artisan of ordinary skill at the time of the invention. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). The court therefore needs to guard against "hindsight bias" that infers from the inventor's success in making the patented invention that the invention was obvious. *In re Cyclobenzaprine*, 676 F.3d at 1079. The ultimate question in the obviousness analysis is "whether there was an apparent reason [for an artisan of ordinary skill] to combine [at the time of the invention] the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. "The analysis is objective." *Id.* at 406. Thus, a court must determine whether an artisan of ordinary skill "would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and . . . would have had a

reasonable expectation of success [in] doing so." *In re Cyclobenzaprine*, 676 F.3d at 1069.

The party challenging the patent's validity bears the burden of proving obviousness by clear and convincing evidence. *Id.* at 1068–69. In weighing the *Graham* factors to decide whether the party has met that burden, the district court must be guided by common sense. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238 (Fed. Cir. 2010). Indeed, "the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony." *Id.* at 1239. In *KSR*, the Supreme Court warned lower courts to avoid "[r]igid preventative rules that deny factfinders common sense" and to employ instead "an expansive and flexible approach" under the *Graham* framework. *KSR*, 550 U.S. at 415, 421. Thus, the district court may "reorder[ ] in any particular case" the "sequence" in which it considers the *Graham* factors. *Id.* at 407. And although a court should consider carefully the published prior art, "[t]he obviousness analysis cannot be confined by . . . overemphasis on the importance of published articles and the explicit content of issued patents." *Id.* at 419.

"[A]ny need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. And "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more

than yield predictable results." *Id.* at 416. "[T]he fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* at 421. But a combination is obvious to try only "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions" in the prior art at the time of the invention. *Id.* And the court must also be mindful that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 416.

B. Issues on Remand

As noted above, the claimed MPH extended release products are (1) liquid formulations with (2) a single mean peak PK profile, (3) an extended duration of effect of about 12 hours, and one or both of (4) an onset of action within 45 minutes and (5) a T_{max} range of about 4 to 5.25 hours. The asserted claims and these five properties are listed in the following chart. An "x" indicates that the claim recites the property in question.

	#765 Pat. Cl. 6	#765 Pat. Cl. 20	#033 Pat. Cl. 4	#033 Pat. Cl. 10	#390 Pat. Cl. 15	#390 Pat. Cl. 16	#390 Pat. Cl. 20
Liquid formulation	X	X	X	X	X	X	X
Single mean peak PK profile	X	X	X	X	X	X	X
12-hour duration	X	X	X	X	X	X	X
T_{max} range of 4–5.25 hours	X		X	X	X	X	X
Onset within 45 minutes		X		X			

There are therefore three combinations relevant to the obviousness analysis: (1) a liquid formulation of MPH with a single mean peak, 12-hour duration , and a the claimed T_{max} range; (2) a liquid MPH formulation with a single mean peak, 12-hour duration, and 45-minute onset; and (3) a liquid MPH formulation with a single mean peak, 12-hour duration, the claimed T_{max} range, and 45-minute onset. For each of these combinations, the issue on remand is whether Actavis has demonstrated by clear and convincing evidence that an artisan of ordinary skill would have been motivated to achieve the combination in question and would have had a reasonable expectation of success in doing so.

C. Findings of Fact

1. Priority Date

The original judge did not make an explicit finding about the priority date of the claimed inventions. He did, however, discuss the scope of the prior art as of July 2010, *see Tris I*, 276 F. Supp. 3d at 237–38, the date Tris claims the invention was reduced to practice, *see* D.I. 151 ¶ 10. Actavis argued for a priority date of February 15, 2011, based on the filing date of a Patent Cooperation Treaty patent application. D.I. 141-3 at 45.[1] But it agrees that the obviousness analysis is the same regardless of which priority date I choose. Accordingly, I will apply a July 2010 priority date.

2. Definition of the Artisan of Ordinary Skill

The original judge found, and I agree, that an artisan of ordinary skill

> would have an advanced degree in pharmaceutical, chemical, or medical sciences (or the equivalent) and 3 to 5 years working in the field(s) of pharmaceutical formulation and/or treatment of conditions susceptible to treatment with methylphenidate. [An artisan of ordinary skill] would also rely as needed on pharmacokineticists and clinicians who have at least 3 to 5 years' experience with ADHD and would have the ability to understand work presented and published by pharmacokineticists and clinicians regarding ADHD.

Tris I, 276 F. Supp. 3d at 250–51.

[1] This pinpoint citation refers to the page number given to the document by CM/ECF and not the original page number appearing at the bottom of the page.

3. Content of the Prior Art

The prior art consists of (1) five commercially available, second-generation extended release MPH formulations; (2) an oral extended release MPH formulation taught in a patent application filed by Scicinski (U.S. Patent Application Publication No. 2010/0260844); (3) a first-generation, immediate release, liquid MPH formulation sold under the brand name Methylin® OS; (4) immediate release and first-generation non-liquid MPH formulations; and (5) scientific articles available as of July 2010. The five commercially available extended release formulations, none of which are liquid, are Concerta®, Daytrana®, Focalin XR®, Metadate CD®, and Ritalin LA®. *Tris II*, 755 F. App'x at 985.

a. Concerta® (JTX-023)

The parties agree that Concerta® is an extended release MPH tablet, D.I. 141-1 ¶ 163, with a 12-hour duration of effect, D.I. 141-1 ¶ 182, and a T_{max} of around 6.8 hours ± 1.8 hours, D.I. 141-1 ¶ 164, which overlaps with the claimed T_{max} range. Actavis argues that Concerta® has a single mean PK profile and a 45-minute onset of action, but I disagree.

I find that Concerta® has a bimodal, not a single peak, PK profile. Concerta®'s mean plasma concentration graph shows two peaks, occurring around two and six hours after administration:

FIGURE 1

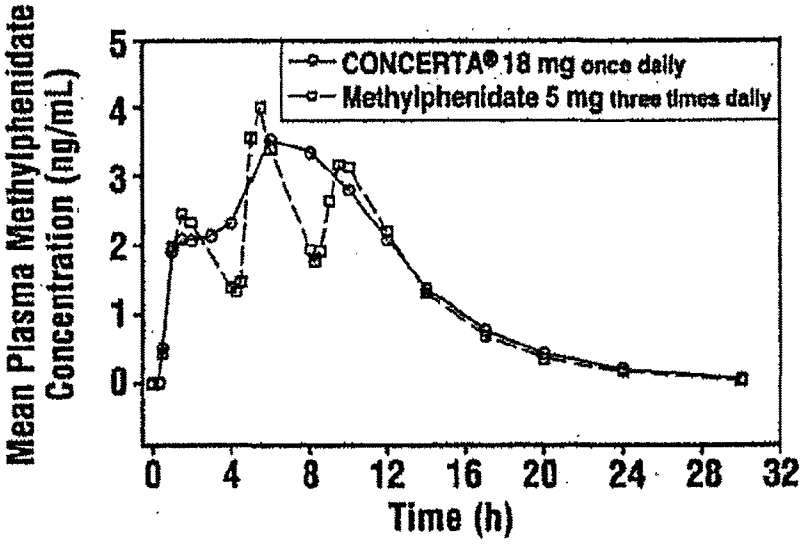

Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA® 18 mg once daily and immediate-release methylphenidate 5 mg three times daily administered every 4 hours.

JTX-023_0005. This graph is consistent with Concerta®'s label, which states that Concerta® displays "an initial maximum . . . followed by gradual ascending concentrations . . . after which a gradual decrease begins." *Id.* Two prior art references also characterize Concerta® as displaying a bimodal plasma concentration profile. An article by González states that "[t]he plasma concentration-time profiles for . . . [Concerta®] exhibited biphasic characteristics, regardless of dosage, consisting of a sharp initial increase followed by a second increase in MPH plasma levels—resulting in two peak plasma concentrations (C_{max-1} and C_{max-2})." JTX-032_0005. And an article by Biederman states that Concerta® exhibits an "[a]scending pattern," and further describes Concerta® as

"display[ing] bimodal patterns representing early and late release of medication." JTX-019_0002.

The only evidence Actavis adduced in support of its contention that Concerta® has a single-peak PK profile was the testimony of its clinical expert, Dr. Staller. I am not persuaded by that testimony for three reasons. First, before this litigation ensued, Dr. Staller had described Concerta® as having two peaks. *See* Tr. at 293:16–18. Second, his trial testimony is flatly contradicted by the graph, prescribing information, González, and Biederman. Third, Dr. Staller testified that he based his opinion that Concerta® has a single-peak profile on the fact that Concerta®'s label reports only one T_{max} and only one C_{max}. But Actavis's PK expert, Dr. Straughn, testified at trial that a single T_{max} may be reported for a product with two peaks. Tr. at 402:13–403:8.

I also find that Concerta® does not achieve onset of therapeutic effect within 45 minutes. The classroom clinical efficacy study disclosed in Concerta®'s label demonstrates that Concerta® shows onset of effect at two hours:

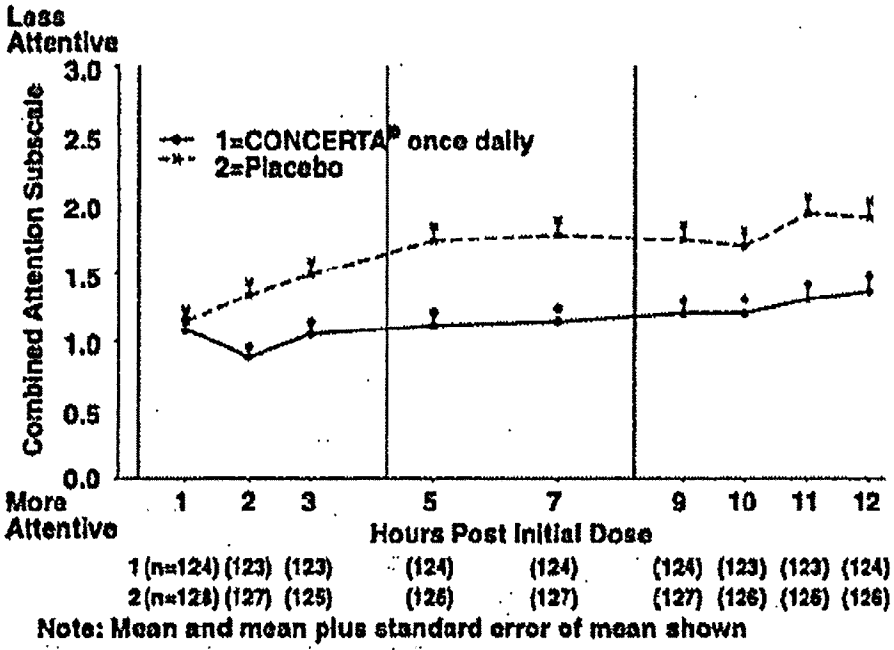

Figure 3: Laboratory School Teacher SKAMP Ratings: Mean (SEM) of Combined Attention (Studies 1 and 2)

JTX-023_0006; *see also* Tr. at 704:14–25.

Actavis points to (1) Dr. Staller's testimony that "30 minutes to two hours is sort of the standard description of the onset of action," Tr. at 276:8–14, and (2) a statement in Biederman that Concerta®'s onset is "30 minutes–2 hours." These statements, however, are flatly contradicted by the label evidence. In short, such statements do not constitute clear and convincing evidence that Concerta®'s onset occurs within 45 minutes.

b. Daytrana® (JTX-025)

Daytrana® is a controlled release MPH skin patch that, when applied for nine hours, has a 12-hour duration of effect and exhibits a two-hour onset of action. JTX-025_0001–02. Daytrana® displays a single mean peak plasma profile, *Tris I*,

276 F. Supp. 3d at 254–55, and exhibits a T_{max} that ranges from 7.5 to 10.5 hours, JTX-025_0002 (Daytrana®'s prescribing information).[2]

c. Focalin XR® (JTX-031)

Focalin XR® is an extended release MPH capsule that achieves a 12-hour duration of effect, JTX-031_0001, 0005; Tr. at 667:13–14; 276:15–18, and an onset of action within 45 minutes, JTX 031_0005. Focalin XR®'s PK profile is bimodal. D.I. 141-1 ¶ 171. It has a T_{max} at 6.5 hours, with a range between 4.5 to 7 hours, which overlaps with the claimed T_{max} range. JTX-031_0004; Tr. at 876:18–877:8.

d. Metadate CD® (JTX-041)

Metadate CD® is a capsule version of MPH, D.I. 141-1 ¶ 166, that has a T_{max} of about 4.5 hours, which falls within the claimed T_{max} range, JTX-041_0001; Tr. at 877:12–15. Metadate CD® has an onset of action within 45 minutes, Tr. at 667:11–12, but its duration of effect is six to eight hours, Tr. at 276:15–20; 667:11–12.

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[2] Daytrana®'s prescribing information is the only evidence in the trial record that discusses the drug's T_{max}. The parties did not discuss Daytrana®'s T_{max} in their post-trial (D.I. 151; D.I. 152) and remand (D.I. 180; D.I. 181) briefs. Daytrana®'s prescribing information indicates that Daytrana®'s T_{max} ranges from 7.5 to 10.5 hours: "Daytrana™ mean peak *d*-MPH concentrations were approximately 1.9-fold higher than the highest observed concentrations after a once-daily oral methylphenidate formulation over a period of 7.5 to 10.5 hours, when T_{max} typically occurs." JTX-025_0002.

The parties dispute whether Metadate CD® has a single mean peak PK profile. Actavis argues that Metadate CD® discloses a single mean peak. But Metadate CD®'s label identifies two peaks. JTX-041_0001 ("METADATE CD has a plasma/time concentration profile showing two phases of drug release with a sharp, initial slope similar to a methylphenidate immediate-release tablet, and a second rising portion approximately three hours later, followed by a gradual decline"). Two pieces of prior art also teach that Metadate CD® is bimodal. González teaches that Metadate CD® exhibits "biphasic characteristics." JTX032_0005. Scicinski also describes Metadate CD® as bimodal. JTX-050 ¶ 60 ("Metadate CD . . . ha[s] bimodal kinetics and ha[s] a higher second plasma peak."). And Actavis's clinical expert, Dr. Staller, described Metadate CD® as bimodal in articles he published before this litigation. Tr. at 331:2–23. Accordingly, I find that Metadate CD® did not disclose a single peak PK profile.

e. Ritalin LA® (JTX -048)

Ritalin LA® is a capsule MPH product, D.I. 141-1 ¶ 174, that displays a bimodal PK profile, Tr. at 707:14–708:15; 321:6–11. Its T_{max} is 5.5 ± 0.8 hours, *see* JTX-048_0003; JTX-038_0007, which falls within the claimed T_{max} range; and it has onset of action that occurs within 45 minutes of administration, D.I. 180 at 29; D.I. 181 at 10. But its duration of effect is six to eight hours. Tr. at 709:4–6; 276:15–19.

f. The Scicinski Patent Application (JTX-050)

Scicinski describes a hypothetical MPH formulation with a single mean PK peak. *Tris I*, 276 F. Supp. 3d at 256. Although Scicinski discloses an oral MPH medication, it never specifically discusses a liquid product. *See* JTX-050. The parties dispute whether Scicinski's formulation has a 45-minute onset of action. Actavis contends that the testimony of its PK expert, Dr. Straughn, established that Scicinski disclosed a 45-minute onset. But the testimony in question reads as follows:

> Q. So were you aware that . . . Scicinski . . . reports that he is expecting a 1 to 1.5 hour onset of action?
>
> A. He says action within about 1 to 1.5 hours. *So that could be*, if you say within an hour, it could be 45 minutes.
>
> Q. *You don't know, one way or another?*
>
> A. *No*. Well, it says within, about. And *I can say that he would like 45 minutes*. In fact, he would like 30 minutes *if he could.*
>
> Q. Would I be reading it fairly if it could also be between 1 and 1 and-a-half hours based on Scicinski?
>
> A. He felt that *they could probably* market a product that measures a therapeutic response between 1 and 1 and-a-half hours. He *probably felt they could* market it that if they could get it on the market.
>
> Q. And *we don't know [whether] he . . . actually* [could achieve 1 to 1.5 hours] because, again, we don't have clinical data to find out?

A. We are talking theoretical here, yes.

Tr. at 408:21–409:13 (emphasis added). Such equivocal testimony does not establish that Scicinski teaches a 45-minute onset. Indeed, I understand Dr. Straughn to be saying that Scicinski aspired for a target onset range of 1 to 1.5 hours that *might* be achieved and *if* it were achieved it *could also possibly* extend to 45 minutes. Accordingly, I find that Scicinski's onset of action is between 1 to 1.5 hours.

The parties also dispute whether Scicinski taught a T_{max} as early as 5.5 hours to achieve a 12-hour duration of effect. Scicinski's written description discloses two T_{max} ranges, each of which corresponds to a different duration-of-effect range. *See* JTX-050 at ¶¶ 15–16 (describing a T_{max} range of 5.5 to 7.5 hours that corresponds to a duration of effect lasting 11 to 12 hours); *see also id.* ¶ 16 (describing T_{max} range of 6 to 7 hours that corresponds to a duration of effect lasting 12 to 14 hours). The description of Figure 7 in Scicinski confirms this correspondence. Figure 7 depicts "[t]he novel and unique in vivo [MPH] release kinetics provided by the oral controlled release dosage forms of the present invention." *Id.* ¶ 61. According to Scicinski, that depiction includes a T_{max} of "about 5.5 to 7.5 hours" and a duration of effect "through at least about 11 to 12 hours" post-administration. *Id.* Thus, I find that Scicinski discloses two

hypothetical MPH formulations. One has a duration of effect that lasts 11 to 12 hours with a corresponding T_{max} range of 5.5 to 7.5 hours; the other has a duration of effect that lasts 12 to 14 hours with a corresponding T_{max} range of 6 to 7 hours.

The testimony of Actavis's pharmacokinetics expert, Dr. Straughn, further supports this finding. Although Dr. Straughn disavowed the notion that Scicinski taught that the T_{max} "needed" to occur at 6 to 7 hours to yield a 12 to 14-hour duration of effect, *see* Tr. at 406:22–407:4, he confirmed that Scicinski disclosed an 11 to 12-hour duration of effect and a corresponding 5.5 to 7.5-hour T_{max} range *see* Tr. at 406:4–10, and a 12 to 14-hour duration of effect and a corresponding 6 to 7-hour T_{max} range, *see* Tr. at 406:15–18. Actavis's clinical expert, Dr. Staller, also testified to this effect:

> Q: So can you explain what Scicinski says in words [to] relate to what he shows in Figure 7 in pictorial form?
>
> A: Well, in his narrative, he gives three different parts. . . . And then [in] the second part, he describes . . . to provide therapeutically effective amount of methylphenidate from 11 to 12 hours . . . . The third component of his description would be a single T_{max} of about 5 and-a-half to 7 and-a-half hours post-administration . . . .
>
> Q: So is the written description in Scicinski, is that consistent with the target profile of Figure 7?
>
> A: Yes, it is.

Tr. at 285:14–286:7. In light of this evidence, I find that Scicinski discloses an MPH formulation exhibiting a T_{max} as early as 5.5 hours, which overlaps with the claimed T_{max} range. I also find Scicinski discloses a formulation with a duration of effect of 11 to 12 hours.

g. Methylin® Oral Solution (JTX-043)

Methylin® OS is the first and only liquid solution of MPH approved in the United States prior to Quillivant®. Tr. at 427:5–10; 671:1–3. Methylin® OS is an IR product, Tr. at 301:25–302:1, and has a single mean peak, *see* D.I. 141-1 ¶ 180. As an IR product, Methylin® OS's duration of effect is short—between three to four hours. JTX-021_0005; Tr. at 671:20–22. Its T_{max} is between one and two hours. JTX-043_0002; Tr. at 396:1–8. The record is silent with respect to Methylin OS®'s onset of action.

4. Comparison of Claimed Limitations with the Prior Art

Based on the above findings, it can be said that each of the five properties in question was disclosed by at least one prior art reference. It is also the case that, other than Scicinski and Focalin XR®, no prior art reference disclosed a combination of more than two of the properties. Scicinski and Focalin XR® each disclosed a combination of three of the properties. The following chart depicts for each prior art reference whether that reference discloses the relevant claim elements of the asserted patents:

	Liquid formulation	Single mean peak	12-hour duration	T_{max} range of about 4–5.25 hours	45-minute onset
Concerta®	No	No	Yes	Yes	No
Daytrana®	No	Yes	Yes	No	No
Focalin XR®	No	No	Yes	Yes	Yes
Metadate CD®	No	No	No	Yes	Yes
Ritalin LA®	No	No	No	Yes	Yes
Scicinski patent	Unclear	Yes	Yes	Yes	No
Methylin OS®	Yes	Yes	No	No	Unclear

5. A liquid MPH formulation with a single mean peak, 12-hour duration, and 45-minute onset

I turn, then, to whether Actavis has shown by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success a liquid MPH formulation with a single mean peak PK profile, 12-hour duration of effect, and 45-minute onset of action. I begin with this combination as opposed to the other two combinations because the Federal Circuit did so in its opinion.

a. Motivation

Although Actavis bears the burden of demonstrating invalidity by clear and convincing evidence, the vast majority of the section of its brief titled "Motivation for a Skilled Artisan To Use a Single Mean Peak PK Profile To Achieve a Formulation with Onset of Action Within 45 Minutes and About 12 Hours of Effect, with a Reasonable Expectation of Success" consists of rebuttal arguments

to counter what Actavis anticipated Tris would argue in its own briefing. Actavis makes three abbreviated affirmative arguments in support of its position. These arguments are confusing and conflicting. And they do not persuade me that Actavis has met its burden to demonstrate by clear and convincing evidence that an artisan of ordinary skill would have been motivated to develop a liquid MPH formulation with a single mean peak, 12-hour duration, and 45-minute onset.

Actavis's first argument is three-pronged:

> In considering motivation, it is significant that [1] the parties *stipulated* that "a POSA would have been motivated to make a liquid [extended-release] methylphenidate formulation that had an early onset of action (e.g., 45 minutes) and efficacy that lasted throughout the day (e.g., 12 hours)." D.I. 161 at 13 (¶ 97). . . . [2] Thus, the only question regarding motivation left open is whether [an artisan of ordinary skill] also would have been motivated to use a formulation that produced a single peak profile. [3] The trial record clearly supports [the original judge's] affirmative answer.

D.I. 181 at 18 (ellipses and numbering added; remaining alterations and italics in original). The second prong of this argument is simply incorrect. The question "left open" as a result of the parties' stipulation is not whether an artisan of ordinary skill would have been motivated to use a single peak profile in "a formulation" (i.e., any liquid MPH formulation). Rather, the question is whether an artisan of ordinary skill would have been motivated to combine a single peak profile with the formulation covered by the stipulation—i.e., a liquid MPH

formulation with a 12-hour duration and 45-minute onset. The fact that an artisan of ordinary skill would have been motivated to make a formulation with a single peak profile is relevant to, but not dispositive of, that inquiry. Assuming *arguendo* that this fact were established, it would not by itself constitute clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine a single peak profile with a liquid MPH formulation that has both a 12-hour duration and 45-minute onset.

The third prong of the argument—that "[t]he trial record clearly supports [the original judge's] affirmative answer"—is problematic for at least two reasons. First, the original judge did not give an affirmative answer to the stated question. Indeed, the Federal Circuit expressly found that the original judge "d[id] not address . . . why [an artisan of ordinary skill] would have been motivated to use a single mean peak PK profile to achieve a formulation with a 45-minute onset of action and[] a 12-hour duration of effect . . . ." *Tris II*, 755 F. App'x at 990. Second, Actavis does not point to anything in the record that supports the conclusion that an artisan of ordinary skill "would have been motivated to use a formulation that produced a single peak profile."

On the contrary—and this is where things get really confusing—Actavis next states in the opening line of its second affirmative argument that its own expert, Dr. Staller, established at trial "that [an artisan of ordinary skill] *would not*

have been concerned about the specific shape of the PK curve—[because] clinical effects [i.e., PD characteristics as opposed to PK characteristics] are what matter." D.I. 181 at 18 (emphasis added). In other words, according to Actavis, its own expert established at trial that an artisan of ordinary skill would have been indifferent (i.e., would have lacked motivation) to use a formulation that produced a single peak profile.[3]

To add to the confusion, in the next two sentences of its brief, Actavis concludes its second affirmative argument as follows:

> Dr. Staller further stated that the goal of [an artisan of ordinary skill] would have been to develop a product with a plasma-release profile that avoids "peaks and valleys" in order to allow "smooth performance" throughout the day. Staller(268:9-269:4, 282:24-283:6). And Dr. Staller explained that a single peak profile could satisfy all of these criteria. Staller (282:24-283:13).

D.I. 181 at 19. These two sentences conflict with the first sentence of the second affirmative argument (i.e., "that [an artisan of ordinary skill] would not have been concerned about the specific shape of the PK curve—[because] clinical effects are what matter"). Actavis appears to be asserting in these two sentences that Dr. Staller testified that an artisan of ordinary skill would have been motivated to

[3] Actavis similarly asserts in its briefing that "the number of peaks would not have been critical to [an artisan of ordinary skill]." D.I. 152 ¶ 72.

develop a liquid MPH formulation with a single peak profile because that profile would "avoid[] peaks and valleys" and allow for a "smooth performance" of the plasma release profile. If that is the case, it not only contradicts the first sentence of Actavis's second argument; it's also undermined by Dr. Staller's own testimony.

Dr. Staller made clear at trial that when he offered opinions about avoiding peaks and valleys and obtaining smooth performance, he was talking about PD, not PK, characteristics. He stated on direct examination that an artisan of ordinary skill would "want a smooth profile" in order to "avoid the peaks and valleys or fluctuations *in terms of the pharmacodynamic or clinical effect* of the drug during the day on patients." Tr. at 283:2–6 (emphasis added). And during cross-examination he testified as follows:

> A. I may have used the term smooth [before]. What I meant was a smooth pharmacodynamic effect, that there wouldn't be disruptions in terms of the clinical effectiveness of the drug over the period of time.
>
> Q. So you weren't referring to a particular pharmacokinetic profile?
>
> A. No, I was not.

Tr. at 308:19–25. Dr. Staller acknowledged at trial that his opinion that a single peak profile could achieve a 12-hour duration and 45-minute onset was based on a "presumption[] that there would be some correlation between the pharmacokinetic profile . . . and the clinical effect[s]" of an MPH formulation. Tr. at 309:9–11; *see*

also Tr. at 309:12 ("I would presume there would be some correlation"). But when asked if he knew whether there is a correlation between the pharmacokinetic effect and the clinical effects for MPH, Dr. Staller admitted: "My experience has been that sometimes there is and sometimes there isn't." Tr. at 309:14–18. In light of that admission, I will not credit Dr. Staller's opinion that an artisan of ordinary skill would have been motivated to use a single peak profile to achieve a 12-hour duration and 45-minute onset.

Dr. Staller's testimony is best read (consistent with the first sentence of Actavis's second affirmative argument) as establishing that an artisan of ordinary skill would *not* have been motivated to use a single mean peak. He testified repeatedly that an artisan of ordinary skill would be indifferent to the shape of the PK profile. *See* Tr. at 328:6–8 ("Q. [D]id the prior art . . . teach to develop a product with a single mean peak? A. I think it could go either way."); 343:3–8 ("Q. [Y]ou don't think there is a motivation to develop a product with any particular curve? A. The particulars of the curve are not the critical issue. The critical issues [are] the [PD characteristics]."); 343:15–344:1 ("The actual number of peaks and their intensity isn't to me the predominant part of this."). This testimony is consistent with the testimony of Dr. Yu-Hsing Tu, one of the inventors of the asserted patents. When asked if he "perceive[d] a benefit to having a single peak profile versus a bimodal profile," Dr. Tu replied, "No." Tr. at

433:8–11. In sum, Dr. Staller's testimony did not establish, let alone by clear and convincing evidence, that an artisan of ordinary skill would have been motivated to use a single peak PK profile in a liquid MPH formulation.

Actavis's third and last affirmative argument with respect to motivation to combine a single peak profile, 12-hour duration, and 45-minute onset in a liquid MPH formulation is more straightforward; but it, too, lacks merits. The argument is that an artisan of ordinary skill "would have been motivated to pursue this [combination] because [the combination had] already appeared in the prior art." D.I. 181 at 19. According to Actavis, "several" of the extended-release prior art references "achieve[d] one or both of [a 12-hour duration and 45-minute onset] with a single mean peak" and Scicinski in particular disclosed "that a formulation with a single mean peak profile can yield both early onset and about 12 hours of effect." *Id.* But as noted above, only two of the extended release prior art references—Daytrana® and Scicinski—disclosed formulations with a single mean peak plasma profile, and neither of those references achieved an onset within 45 minutes. Thus, Actavis is simply wrong as a factual matter that any prior art refence disclosed this combination.

Finally, Actavis dedicated much of its briefing to rebuttal arguments intended to counter Tris's contention that the prior art theory of "acute tolerance" (also known as "tachyphylaxis") taught away—and thus would have dissuaded an

artisan of ordinary skill—from combining a single peak profile with a 12-hour duration and 45-minute onset. Acute tolerance "is the theory that as the day progresses, higher levels of the drug in the blood are required to produce the same therapeutic effects." *Tris II*, 755 F. App'x at 986. Tris's expert, Dr. McGough, testified that the theory led to a shift from single-peak first-generation MPH formulations to bimodal second-generation MPH formulations. Tr. at 676:24–693:25. Actavis's expert, Dr. Staller, acknowledged at trial that "some of the experts in the prior art" argued about the acute tolerance theory and whether that theory taught "against or away from a single peak." Tr. at 353:15–20. He insisted, however, that "there wasn't a teaching away from a single peak." Tr. at 353:21–24.

Because I did not observe the live testimony of the parties' competing experts, I lack the requisite confidence to make a definitive finding about whether the acute tolerance theory teaches away from a single peak PK profile with a 12-hour duration and 45-minute onset. But even if the theory did not teach away from that combination, I would still find that Actavis did not meet its burden to show a motivation to combine a single peak profile with a 12-hour duration and 45-minute onset.

b. Reasonable Expectation of Success

With respect to a reasonable expectation of success, Actavis argues that both Concerta® and Scicinski disclose formulations that embody all the claimed limitations at issue. D.I. 181 at 9–10. But as discussed above, Concerta® does not disclose a single peak profile or a 45-minute onset; and Scicinski does not disclose a 45-minute onset.

Actavis also argues that a patent application published by Mehta taught an artisan of ordinary skill how to develop a liquid formulation of MPH with a single mean peak PK profile, 12-hour duration, and 45-minute onset. D.I. 181 at 14–16. Actavis made this same argument to the original judge, and he found credible Dr. Moreton's testimony that Mehta would have taught a formulator how to achieve an early onset of action and extended duration of effect with a single peak profile as of the priority date. *Tris I*, 276 F. Supp. 3d at 257. I agree with Actavis that "Mehta taught that [a] desired release profile could be achieved by changing the ratio of immediate- and sustained-release components in the formulation." D.I. 181 at 15 (citing JTX-040 at ¶¶ 10–11, 20, 60, 72). But nowhere does Mehta teach or suggest that one can simultaneously achieve the desired early onset of action and extended duration of effect while maintaining a single peak PK profile. Mehta teaches merely that one can develop a desired release profile; it does not suggest that one can achieve specific PD characteristics associated with the desired profile.

See Tr. at 843:17–25 (testimony from Dr. Jacobs that Mehta "provides no helpful information as to, if we did have a single mean peak, it could provide rapid onset as well at 12 hours"). For that reason, even if Dr. Moreton appeared credible to the original judge at trial, I find that his testimony is insufficient to establish by clear and convincing evidence that an artisan of ordinary skill would have had a reasonable expectation of success in developing a liquid MPH formulation with a single mean peak, 12-hour duration, 45-minute onset.

My finding is also informed by my conclusion that the prior art taught away from combining in a liquid MPH formulation a single mean peak, 12-hour duration, and 45-minute onset. I reach this conclusion for three reasons. First, no single peak prior art reference disclosed a 12-hour duration of effect and onset of action within 45 minutes. For example, immediate release MPH—including Methylin® OS—has a single mean peak PK profile but does not meet the 12-hour duration of effect. Tr. at 666:17–21. First-generation MPH products also exhibited a single mean peak but were considered "robust failure[s]" because of their inability to produce an early onset and extended duration of effect. Tr. at 673:25–674:12; *see also* Tr. at 666:17–667:2 (Dr. McGough testifying that first-generation agents such as Ritalin SR® employed a single peak but failed to produce an early onset of action and extended duration of effect); Tr. at 270:8–14 (Dr. Staller testifying that first-generation products were a "disappointment" because

they did not achieve a rapid onset and long-lasting therapeutic effects). Daytrana® and Scicinski employed a single mean peak to achieve a 12-hour duration of effect, but their onsets of action were longer than the claimed 45 minutes.

Second, the only MPH formulation that had achieved both 12-hour duration and 45-minute onset as of July 2010 was Focalin XR®, but Focalin XR® had two peaks. Third, it would have made sense to an artisan of ordinary skill in July 2010 that two or more peaks were required to achieve a combination of early onset and 12-hour duration of effect. Dr. McGough cogently explained at trial why this is so:

> So we need to begin with the understanding that an oral formulation, a capsule or a pill, can only contain so much medication. . . .
>
> If your intention is to use a single mean peak profile and your goal is to obtain 45 minutes of effect, then you will want that peak to be early. But once the medication is released to provide that level, elimination forces will come in and it will rapidly be metabolized out of the system and you won't have sufficient medication later in the day for that effect.
>
> Conversely, you can have a formulation designed to slowly begin absorption of medication so that you have a single peak later in the day that would allow for effect later in the day, if you are lucky, but that wouldn't provide enough medication to provide a response early in the day.
>
> So use of the single mean peak profile therefore can quickly achieve a 45 minute onset but not a 12 hour effect, or can achieve a 12 hour effect but not an earlier onset.
>
> So the solution for getting both the 45 minute and late onset effect is to use formulations that have separate pulses

> of medication that can overcome problems related to elimination and thereby by necessity provide an early peak and a late peak as part of the pharmacokinetic profile.

Tr. at 665:1–666:11.

In short, the prior art taught that multiple peaks, achieved by multiple pulses of medication, were required to achieve both a 12-hour duration and 45-minute onset. Thus, the prior art taught away from use of a single peak to achieve that combination of clinical effects.

c. Secondary Considerations

My findings with respect to motivation and reasonable expectation of success are further supported by the evidence Tris adduced at trial with respect to two secondary considerations: unexpected results and long-felt, unmet need.

Tris's evidence of unexpected results is essentially the same evidence it relied on to rebut Actavis's argument that an artisan of ordinary skill would have had a reasonable expectation of success in combining the single peak profile with a 12-hour duration and 45-minute onset. That evidence, which I have detailed above, supports a finding that the achievement of this combination was an unexpected result.

Tris's evidence of long-felt unmet need as of July 2010 for a liquid MPH formulation with a 12-hour duration and 45-minute onset is especially compelling. The need for such a formulation arose from two undisputed phenomena: (1)

children, the primary focus of ADHD treatment, often have difficulty swallowing pills; and (2) it is much easier for patients generally and children in particular to comply with a therapy regimen that is accomplished with a single daily dose as opposed to multiple doses taken throughout the day. The need was long-felt and unmet because even though MPH had been used to treat ADHD since the mid-1950s, the only two formulations available as of July 2010 that allowed for a single daily dose regimen (i.e., 12-hour duration of effect) and an early onset were Concerta® and Focalin®, and both of those formulations required the swallowing of a pill or capsule. The only liquid formulation available at the time, Methylin® OS, was an immediate release product with a duration of effect that lasted only three to four hours. JTX-021_0005; Tr. at 671:20–22. Daytrana® did not require the swallowing of pills or tablets and met the 12-hour duration need, but it did not have an early onset and the patch it required patients to wear caused significant skin irritation and a risk of poisoning. Scicinski, which was only a hypothetical formulation, apparently satisfied the 12-hour duration requirement but did not have an early onset and did not make clear whether it could be administered as a liquid.

The fact that a liquid MPH formulation with 12-hour duration and 45-minute onset was a long-felt unmet need as of July 2010 exposes the hindsight bias that underlies Actavis's arguments that an artisan of ordinary skill would have been

able to discern from the prior art the road map to achieve the liquid formulation taught in the asserted claims.

6. A liquid MPH formulation with a single mean peak, 12-hour duration, and the claimed T_{max} range

I consider next whether Actavis has shown by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success a liquid formulation of MPH with a single mean peak PK profile, 12-hour duration of effect, and a T_{max} range of about 4 to 5.25 hours. I find that Actavis has not met this burden.

a. Motivation

Although Actavis characterized the question of whether "the prior art provide[d an artisan of ordinary skill] with . . . a motivation to develop an MPH formulation with a T_{max} of 'about' 4 to 5.25 hours and 'about' 12 hours of effect" as "a primary issue[]" for me to address, D.I. 181 at 6, it did not offer in its post-trial or post-remand briefing any argument on this question. *See* D.I. 152; D.I. 181. Accordingly, Actavis failed to establish by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine a liquid MPH formulation with 12-hour duration, single mean peak, and the claimed T_{max} range.

b. Reasonable Expectation of Success

Actavis argues that an artisan of ordinary skill reasonably would have expected to achieve a liquid MPH formula that combined a single mean peak with 12-hour duration and the claimed T_{max} range because Scicinski "*already disclosed* such a formulation." D.I. 181 at 23 (emphasis in original). This argument fails for three reasons.

First, Actavis did not allege, let alone prove by clear and convincing evidence, that Scicinski disclosed a *liquid* MPH formulation. It cannot be disputed that Scicinski disclosed an oral formulation. *See* JTX-050_0001 (describing "controlled release oral dosage forms"). But oral and liquid are two different things. The asserted patents claim only oral formulations that are liquid. Notably, neither Actavis nor its experts have asserted that Scicinski encompasses liquid formulations of MPH. On the other hand, Tris has asserted that Scicinski only describes capsule formulations. *See* (D.I. 180 at 20 (citing JTX-50_0012 and ¶¶ 197–199). With the exception of the Daytrana® patch, every second-generation formulation in the prior art as of July 2010 was administered in the form of a solid oral dose. And, as discussed above, there was a long-felt, unmet need for a liquid formulation precisely because the existing oral formulations that had 12-hour duration of effect were either tablets or capsules and were therefore difficult for many children to swallow.

Second, Scicinski's formulation was never administered to humans and, therefore, no PK or PD data for it existed. As Dr. McGough testified, Scicinski's formulation was

> not a real product. It was aspirational. It was a target profile that he created. And there are absolutely no pharmacokinetic or clinical data to suggest that he would achieve it or that it would have the clinical effects that he intends.

Tr. at 713:15–19. Third, Scicinski did not offer any explanation about why he thought his formulation could achieve a combined a single mean peak with 12-hour duration and a T_{max} range of about 4 to 5.25 hours. For these reasons, I find that Scicinski would not have provided an artisan of ordinary skill with a reasonable expectation of successfully developing this combination. As Dr. McGough testified when asked how an artisan of ordinary skill would "view the Scicinski disclosure?": "[I]t would be dismissed. There are no data. It is a hypothetical target. It's poorly described, and it would have no impact." Tr. at 720:15–19.

c. Secondary Considerations

Tris argues that its "invention unexpectedly provided: . . . a 12 hour effect with [a] T_{max} of about 4 to about 5.25 hours." D.I. 151 ¶ 76. But in support of this contention, it relies exclusively on the fact that the commercially available second-generation products do not include a single-peak formulation with a 12-hour

duration and the claimed T_{max} range. Because there are only five commercially available second-generation products, the fact that none of them taught the combination of an MPH formulation with a single mean peak, 12-hour duration, and the claimed T_{max} range does not by itself warrant a finding that the achievement of that combination was an unexpected result. Had Tris adduced expert testimony that explained why the achievement of this combination was unexpected (as it did with respect to the combination of a single mean peak, 12-hour duration, and 45-minute onset), I might have reached a different conclusion. In any event, the fact that Tris did not prove to my satisfaction that the claimed combination was an unexpected result does not change my opinion that Actavis failed to meet its burden of proving by clear and convincing evidence that an artisan of ordinary skill would have been motivated to develop with a reasonable expectation of success that combination.

7. A liquid MPH formulation with a single mean peak. 12-hour duration, 45-minute onset, and the claimed Tmax range

Because I have already found that an artisan of ordinary skill would not have been motivated to combine with a reasonable expectation of success a liquid MPH formulation with a single mean peak profile, 12-hour duration, and 45-minute onset; it follows necessarily, and I find that, Actavis has not established by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success a liquid MPH

formulation with a single mean peak profile, 12-hour duration, 45-minute onset, and the claimed T_{max} range. Because I find that an artisan of ordinary skill would not have been motivated to combine with a reasonable expectation of success liquid MPH formulation with a single mean peak profile, 12-hour duration, and the claimed T_{max} range; it follows necessarily, and I find that, Actavis has not established by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success a liquid MPH formulation with a single mean peak profile, 12-hour duration, 45-minute onset, and the claimed T_{max} range.

D. Conclusions of Law

1. A liquid MPH formulation with a single mean peak, 12-hour duration, and 45-minute onset

I have already found as a factual matter that Actavis did not prove by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success a liquid MPH formulation with a single mean peak, 12-hour duration, and 45-minute onset. This combination is recited in claim 20 of the #765 patent.

Perhaps because it realizes its failure of proof, Actavis appears to argue on remand that an artisan of ordinary skill would have been indifferent to the choice between a single peak and bimodal peak profile and that this indifference "does not undermine motivation." D.I. 181 at 19–20. According to Actavis, "[t]o establish

obviousness, precedent 'does not require that the [claimed limitation in question] be the best option, only that it be a suitable option from which the prior art did not teach away.'" *Id.* at 20 (quoting *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014)). Here, however, for the reasons discussed above, an artisan of ordinary skill would not have viewed the single peak profile as a suitable option, as the prior art taught away from using a single peak. Accordingly, I conclude as a matter of law that Actavis failed to establish that claim 20 of the #765 patent is invalid as obvious under § 103.

2. A liquid MPH formulation with a single mean peak, 12-hour duration, and the claimed T_{max} range

I have already found as a factual matter that Actavis did not prove by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success a liquid MPH formulation with a single mean peak, 12-hour duration, and the claimed T_{max} range. This combination is recited in claim 4 of the #033 patent, claim 6 of the #765 patent, and claims 15, 16, and 20 of the #390 patent.

Actavis argues in its post-remand brief that because Scicinski discloses the claimed PK and PD limitations, it establishes a presumption of obviousness that the plaintiffs have not rebutted. *See* D.I. 181 at 25. It is true that "[a] *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art." *In re Peterson*, 315 F.3d 1325, 1329

(Fed. Cir. 2003). But the presumption attaches only when "the range or value of a particular variable" is "*the* difference between the claimed invention and the prior art." *Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1577 n.3 (Fed. Cir. 1993) (emphasis added). In this case, the single mean peak, 12-hour duration, and claimed T_{max} range are not individually or collectively the difference between the claimed invention and Scicinski. The asserted claims require that the invention be a liquid formulation of MPH, and Actavis has not alleged, let alone established by clear and convincing evidence, that Scicinski teaches a liquid MPH formulation. Accordingly, Actavis is not entitled to a presumption of obviousness.

My confidence in this conclusion is boosted by the fact that Scicinski was considered by the United States Patent & Trademark Office (PTO) when it approved the asserted claims. D.I. 141-1 ¶ 152; *Tokai Corp. v. Easton Enters.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011) ("[A] party challenging validity shoulders an enhanced burden if the invalidity argument relies on the same prior art considered during examination by the U.S. Patent and Trademark Office . . . .").

I therefore conclude as a matter of law that Actavis has failed to establish that claim 4 of the #033 patent, claim 6 of the #765 patent, and claims 15, 16, and 20 of the #390 patent are invalid as obvious under § 103.

3. A liquid MPH formulation with a single mean peak, 12-hour duration, 45-minute onset, and the claimed T_{max} range

I have already found as a factual matter that Actavis did not prove by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success a liquid MPH formulation with a single mean peak, 12-hour duration, 45-minute onset, and the claimed T_{max} range. Accordingly, I conclude as a matter of law that Actavis failed to establish that claim 10 of the #033 patent is invalid as obvious under § 103.

III. INFRINGEMENT

Actavis has stipulated that its ANDA products satisfy the liquid formulation, 12-hour duration, claimed T_{max} range, and 45-minute onset limitations of the asserted claims. *See* D.I. 141-1 ¶¶ 90, 91, 95, 98, 99, 100, 102–105; D.I. 147 ¶¶ 2–5. Thus, the only dispute regarding infringement is whether Actavis's ANDA products satisfy the single mean peak limitation. Actavis does not challenge Tris's claims for induced and contributory infringement if I find for Tris on direct infringement. D.I. 141-1 ¶ 89.

A. Legal Standards

A defendant is liable for patent infringement if it files an ANDA "for a drug claimed in a patent or the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2)(A). To establish infringement based on the filing of an ANDA under § 271(e)(2)(A), a patentee must show that "if the drug were approved based upon

the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997).

"Conventional" infringement includes direct and induced infringement. 35 U.S.C. § 271(a), (b). Direct infringement requires that "every limitation set forth in a claim . . . be found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995) (citation omitted).

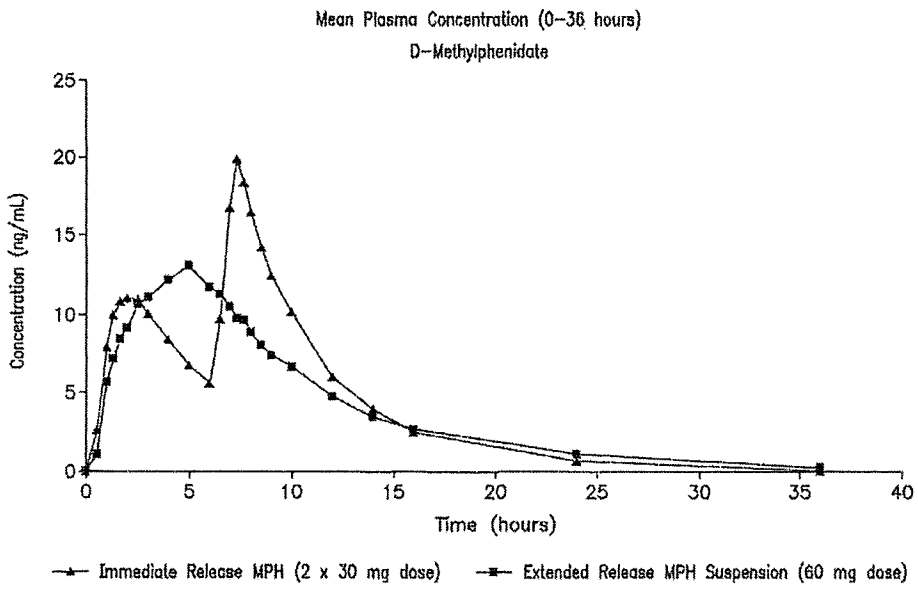
A patentee must prove infringement by a preponderance of the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984). "A patentee may prove infringement by any method of analysis that is probative of the fact of infringement, and circumstantial evidence may be sufficient." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009) (internal quotation marks and citations omitted).

B. Discussion

All the asserted claims either explicitly require or depend from claims that explicitly require "a single mean average plasma concentration peak." The original judge construed this phrase to have its plain and ordinary meaning. D.I. 95 at 1. The judge noted that "the plain and ordinary meaning of the claim language is sufficient to differentiate the covered plasma profiles from plasma

profiles with two distinct peaks arising from two different release components." D.I. 95 at 1 n.2.

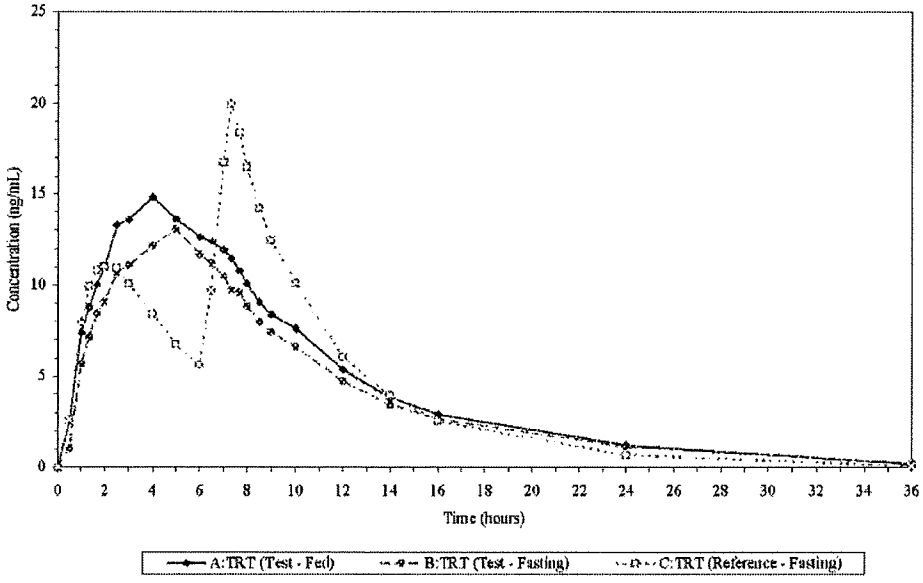
It is undisputed that Actavis's generic MPH formulations have the same plasma profile as Quillivant®. That profile is depicted in graphs found in the labels of Actavis's drug and Quillivant® and in Figure 3 of the written description shared by the asserted patents. The only issue is whether that plasma profile has one or two peaks. Tris's expert on pharmacokinetics, Dr. DeVane, testified that the profile shows a single mean peak. Tr. at 196:10–24; 202:19–203:12; 204:11–18. Dr. Tu, one of the inventors, similarly represented in a sworn declaration filed with the PTO that the profile has a single peak. JTX-7A_0260 (¶ 8). Actavis's expert, Dr. Staller, also conceded at trial that Figure 3 of the patents has a single mean peak. Tr. at 314:15–315:3. And a visual inspection of the three curves confirms that they are the same and have a single peak profile:



JTX-001_0005
(#765 patent)

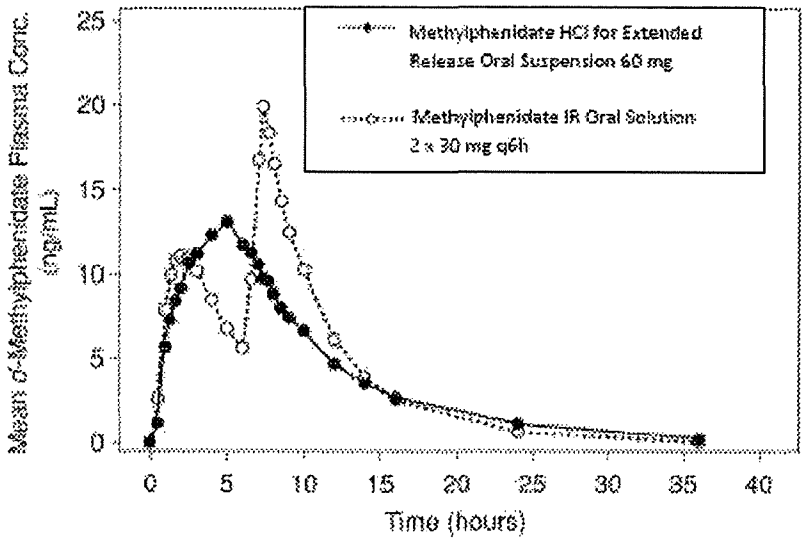
FIG. 3

Figure 2. Mean *d*-Methylphenidate Plasma Concentration-Time Profiles



JTX-016_0007
(Quillivant
Label)

Figure 2. Mean *d*-Methylphenidate Plasma Concentration-Time Profiles



PTX-044_0013 (Actavis ANDA Product)

Based on these facts, I find that Actavis's generic products satisfy the single mean peak limitation.[4]

Actavis's principal attack on this compelling evidence is that Pfizer, which markets Quillivant® for Tris, "put forward [in a 2014 Citizen Petition filed with the United States Food and Drug Administration (FDA)] evidence that Quillivant's plasma profile has *two* peaks—a 'shoulder' with a T_{max} at approximately 1.67–2 hours followed by a second peak with a T_{max} between 4 and 5 hours." D.I. 190 at 4

[4] This finding is further confirmed by the testimony of Drs. DeVane and Jacobs that the PK profiles of Actavis's drugs depicted in two biostudies also show a single mean peak profile. Tr. at 168:5–17; 198:10–24, 199:7–200:14 (analyzing JTX-014, and JTX-015). I am not persuaded by Actavis's arguments that the testimony of Drs. DeVane and Jacobs lacked credibility. And I find Dr. DeVane's testimony in particular to be credible. As discussed above, Dr. DeVane's testimony that Actavis's drugs have a single mean peak is corroborated by Dr. Tu's sworn declaration, Dr. Staller's testimony, and a visual inspection of the relevant PK profiles.

(emphasis in original). Actavis argues that judicial estoppel bars Tris from asserting in this litigation that Quillivant® and, by extension, Actavis's generic products have a single peak profile because that position is inconsistent with Pfizer's position in its Citizen Petition that Quillivant® is bimodal. Actavis argues in the alternative that "Tris's litigation-driven reversal as to the number of peaks in Quillivant®'s plasma profile is not credible." D.I. 190 at 8.

The dispositive flaw in Actavis's arguments is their shared premise—i.e., that Quillivant®'s shoulder with a T_{max} at approximately 1.67 to 2 hours is a peak. The Citizen Petition refers to this feature of the plasma profile only as a shoulder and never as a peak. The parties agree that a shoulder "refers to the region where the rate of increase or decrease in drug plasma concentration slows or flattens for a period of time." D.I. 191 at 11; *see* D.I. 190 at iv. And Tris acknowledges that a shoulder can be a peak. But Tris's expert, Dr. Jacobs, testified that a shoulder can be a peak only if it is followed by a second accelerating phase of drug release. Tr. at 183:11–184:3; *see also* Tr. at 177:3–18 (describing a shoulder as a peak when followed by "an extended ascending phase leading to a maximum"). And Dr. Jacobs further testified that no second accelerating phase is present in the data presented in Pfizer's Citizen Petition. Tr. at 184:5–9 ("[The Citizen Petition] talks about a shoulder, but it does not talk about [a] second acceleration which . . . is not evident in the curve shown this morning."). Actavis presented no expert of its own

to rebut Dr. Jacob's testimony, and I find that testimony to be credible. Thus, the shoulder identified in the Citizen Petition is not a peak.

I find therefore that Tris has demonstrated by a preponderance of the evidence that Actavis's generic product meets the single mean peak limitation found in the asserted claims. Given Actavis's stipulations with respect to the other limitations of the asserted claims, I find Actavis liable for direct, induced, and contributory infringement of the asserted claims as a matter of law.

IV. CONCLUSION

For the foregoing reasons, I find that all the asserted claims of the asserted patents before me on remand are not invalid and that Defendants directly infringe, contributorily infringe, and induce the infringement of each of the asserted claims.

The parties will be directed to submit a proposed order by which the Court may enter final judgment consistent with this Opinion.